

# Northumbria Research Link

Citation: Angius, Luca and Crisafulli, Antonio (2020) Exercise intolerance and fatigue in chronic heart failure: is there a role for group III/IV afferent feedback? *European Journal of Preventive Cardiology*, 27 (17). pp. 1862-1872. ISSN 2047-4873

Published by: SAGE

URL: <https://doi.org/10.1177/2047487320906919>  
<<https://doi.org/10.1177/2047487320906919>>

This version was downloaded from Northumbria Research Link:  
<http://nrl.northumbria.ac.uk/id/eprint/42563/>

Northumbria University has developed Northumbria Research Link (NRL) to enable users to access the University's research output. Copyright © and moral rights for items on NRL are retained by the individual author(s) and/or other copyright owners. Single copies of full items can be reproduced, displayed or performed, and given to third parties in any format or medium for personal research or study, educational, or not-for-profit purposes without prior permission or charge, provided the authors, title and full bibliographic details are given, as well as a hyperlink and/or URL to the original metadata page. The content must not be changed in any way. Full items must not be sold commercially in any format or medium without formal permission of the copyright holder. The full policy is available online: <http://nrl.northumbria.ac.uk/policies.html>

This document may differ from the final, published version of the research and has been made available online in accordance with publisher policies. To read and/or cite from the published version of the research, please visit the publisher's website (a subscription may be required.)



**Northumbria**  
**University**  
NEWCASTLE



**UniversityLibrary**

# European Journal of Preventive Cardiology

## Exercise intolerance and fatigue in chronic heart failure: is there a role for group III/IV afferent feedback? --Manuscript Draft--

<b>Manuscript Number:</b>	EJPC-D-19-01314R2
<b>Full Title:</b>	Exercise intolerance and fatigue in chronic heart failure: is there a role for group III/IV afferent feedback?
<b>Article Type:</b>	Review
<b>Section/Category:</b>	Cardiovascular Disease
<b>Corresponding Author:</b>	Luca Angius, PhD Northumbria University Newcastle upon Tyne, Tyne and Wear UNITED KINGDOM
<b>Corresponding Author Secondary Information:</b>	
<b>Corresponding Author's Institution:</b>	Northumbria University
<b>Corresponding Author's Secondary Institution:</b>	
<b>First Author:</b>	Luca Angius, PhD
<b>First Author Secondary Information:</b>	
<b>Order of Authors:</b>	Luca Angius, PhD Antonio Crisafulli
<b>Order of Authors Secondary Information:</b>	
<b>Manuscript Region of Origin:</b>	UNITED KINGDOM
<b>Abstract:</b>	<p>Exercise intolerance and early fatigability are hallmark symptoms of chronic heart failure (CHF). While the malfunction of the heart is certainly the leading cause of CHF, the patho-physiological mechanisms of exercise intolerance in these patients are more complex, multifactorial, and only partially understood. Some evidences point towards a potential role of an exaggerated afferent feedback from group III/IV muscle afferents in the genesis of these symptoms. Overactivity of feedback from these muscle afferents may cause exercise intolerance with a double action: by inducing cardiovascular dysregulation, by reducing motor output, and by facilitating the development of central and peripheral fatigue during exercise. Importantly, physical inactivity appears to negatively affect the progression of the syndrome, while physical training can partially counteract this condition. In the present review, the role played by the group III/IV afferents feedback in the cardiovascular regulation during exercise and exercise-induced muscle fatigue of healthy people and their potential role in inducing exercise intolerance in CHF patients will be summarised.</p>

### ***Note to Reviewers***

We would like to thank both Reviewers for their thorough and considered review of our manuscript. We found all the comments to be thoughtful and constructive, and have allowed us to make some significant improvements to the manuscript. We hope these amendments are to your satisfaction. We have replied to each comment in this document (in red), and where a manuscript amendment was required, we have highlighted the changed text in yellow (added/revised words or sections) and in red (deleted) within the manuscript file. We hope you enjoy reading the revised version of the manuscript.

### **Reviewer #1:**

This is an important and interesting review. The manuscript is very well designed and written. However, I suggest that the authors included a section about the effects of exercise training on group-III/IV receptors and/or mechano and metaboreflex.

**AUTHORS:** we really thank the reviewer for this useful comment. As suggested, we included a section “Exercise training as therapy for chronic heart failure patients” describing the general guidelines and effect of aerobic and resistance training on CHF as well as its potential beneficial effect on EPR.

### **Reviewer #2:**

There are some questions to explain about the article «Exercise intolerance and fatigue in CHF: is there a role for group III/IV afferent feedback?»:

- Could you give an explanation about the relationship of this afferent feedback with the respiratory response?
- Is there any role for the diaphragmatic muscle in this afferent feedback?
- If so, have you reviewed the role of the respiratory training in this field/inspiratory muscle threshold?
- Could you give more information about the benefit of resistance training vs endurance training (continuous/intervalic)?

**AUTHORS:** we really thank the reviewer for these useful comments. We have included a section called “Exercise training as therapy for chronic heart failure patients” in which we described the effect of different types of training on physical capacity of CHF patient. In the same section we also included how these can reduce the exaggerated activity of peripheral muscle afferents.

## References

1. Chiappa GR, Roseguini BT, Vieira PJ, Alves CN, Tavares A, Winkelmann ER, et al. Inspiratory muscle training improves blood flow to resting and exercising limbs in patients with chronic heart failure. *J Am Coll Cardiol*. 2008;51(17):1663-71.
2. Downing J, Balady GJ. The role of exercise training in heart failure. *J Am Coll Cardiol*. 2011 Aug 2;58(6):561-9. doi: 10.1016/j.jacc.2011.04.020.
3. Laoutaris ID, Dritsas A, Brown MD, Manginas A, Kallistratos MS, Chaidaroglou A, Degiannis D, Alivizatos PA, Cokkinos DV. Effects of inspiratory muscle training on autonomic activity, endothelial vasodilator function, and N-terminal pro-brain natriuretic peptide levels in chronic heart failure. *J Cardiopulm Rehabil Prev*. 2008 Mar-Apr;28(2):99-106. doi: 10.1097/01.HCR.0000314203.09676.b9.
4. Mancini DM, Henson D, La Manca J, Donchez L, Levine S. Benefit of selective respiratory muscle training on exercise capacity in patients with chronic congestive heart failure. *Circulation*. 1995 Jan 15;91(2):320-9.
5. Meyer FJ, Borst MM, Zugck C, Kirschke A, Schellberg D, Kübler W, Haass M. Respiratory muscle dysfunction in congestive heart failure: clinical correlation and prognostic significance. *Circulation*. 2001 May 1;103(17):2153-8.
6. Notarius CF, Millar PJ, Keir DA, Murai H, Haruki N, O'Donnell E, Marzolini S, Oh P, Floras JS. Training Heart Failure Patients With Reduced Ejection Fraction Attenuates Muscle Sympathetic Nerve Activation During Mild Dynamic Exercise. *Am J Physiol (Regul Integr Comp Physiol)* 2019; 317 (4): R503-R512.
7. Piepoli M, Clark AL, Volterrani M, Adamopoulos S, Sleight P, Coats AJ. Contribution of Muscle Afferents to the Hemodynamic, Autonomic, and Ventilatory Responses to Exercise in Patients With Chronic Heart Failure: Effects of Physical Training. *Circulation* (1996); 93 (5): 940-952.
8. Piepoli MF, Conraads V, Corrà U, Dickstein K, Francis DP, Jaarsma T, McMurray J, Pieske B, Piotrowicz E, Schmid JP, Anker SD, Solal AC, Filippatos GS, Hoes AW, Gielen S, Giannuzzi P, Ponikowski PP. Exercise training in heart failure: from theory to practice. A consensus document of the Heart Failure Association and the European Association for Cardiovascular Prevention and Rehabilitation. *Eur J Heart Fail*. 2011 Apr;13(4):347-57. doi: 10.1093/eurjhf/hfr017.
9. Sheel AW, Boushel R, Dempsey JA. Competition for blood flow distribution between respiratory and locomotor muscles: implications for muscle fatigue. *J Appl Physiol* (1985). 2018 Sep 1;125(3):820-831. doi: 10.1152/jappphysiol.00189.2018. Epub 2018 Jun 7.
10. Supinski JS, Callahan LA: Diaphragmatic free radical generation in an animal model of heart failure. *J Appl Physiol* 2005, 99:1078–1084.
11. Wang HJ, Zucker IH, Wang W. Muscle reflex in heart failure: the role of exercise training. *Front Physiol* 2012a; 3, 398. DOI: 10.3389/fphys.2012.00398
12. Winkelmann ER, Chiappa GR, Lima CO, Viegili PR, Stein R, Ribeiro JP. Addition of inspiratory muscle training to aerobic training improves cardiorespiratory responses to exercise in patients with heart failure and inspiratory muscle weakness. *Am Heart J*. 2009 Nov;158(5):768.e1-7. doi: 10.1016/j.ahj.2009.09.005. Epub 2009 Oct 2.

Luca Angius<sup>1</sup>, Antonio Crisafulli<sup>2</sup>

**Exercise intolerance and fatigue in chronic heart failure: is there a role for group III/IV afferent feedback?**

**Affiliation:**

<sup>1</sup> Faculty of Health and Life Sciences, Sport, Exercise and Rehabilitation, Northumbria University, Newcastle-upon-Tyne, United Kingdom.

<sup>2</sup> Department of Medical Sciences and Public Health, Sports Physiology Lab., University of Cagliari, Cagliari, Italy.

**Corresponding author:**

Dr. Luca Angius

Faculty of Health and Life Sciences,  
Department of Sport, Exercise and Rehabilitation,  
Northumbria University,  
Newcastle-upon-Tyne,  
NE1 8ST,  
UK

Tel: +44 (0) 0191 227 4564

Email: luca.angius@northumbria.ac.uk

**Word count:** 4995 words

## Abstract

Exercise intolerance and early fatigability are hallmark symptoms of chronic heart failure (CHF). While the malfunction of the heart is certainly the leading cause of CHF, the pathophysiological mechanisms of exercise intolerance in these patients are more complex, multifactorial, and only partially understood. Some evidences point towards a potential role of an exaggerated afferent feedback from group III/IV muscle afferents in the genesis of these symptoms. Overactivity of feedback from these muscle afferents may cause exercise intolerance with a double action: by inducing cardiovascular dysregulation, by reducing motor output, and by facilitating the development of central and peripheral fatigue during exercise. Importantly, physical inactivity appears to negatively affect the progression of the syndrome, while physical training can partially counteract this condition. In the present review, the role played by the group III/IV afferents feedback in the cardiovascular regulation during exercise and exercise-induced muscle fatigue of healthy people and their potential role in inducing exercise intolerance in CHF patients will be summarised.

**Keywords:** Metabo-reflex, Fatiguability, Circulation, Exercise pressor reflex, Sensory neurons, Muscle fatigue.

## Introduction

Exercise intolerance and early fatigability are hallmark symptoms of chronic heart failure (CHF). These symptoms severely limit daily activities and have been traditionally considered as the consequence of the inability of the heart to meet the metabolic demand of the muscles during exercise, with the malfunction of the heart as a pump as the leading cause <sup>1</sup>. However, the pathophysiological mechanisms of exercise intolerance in CHF are more complex, multifactorial, and only partially investigated and understood.

At heart level, the combination of systolic and diastolic abnormalities concurs in reducing the capacity to increase cardiac output (CO). Moreover, several other abnormalities such as impairments in peripheral endothelial-dependent vasodilation, reduction in systemic oxygen delivery, reduction in pulmonary reserve, and respiratory muscle perfusion have all been observed and they potentially account for the reduced exercise capacity in this syndrome <sup>2-5</sup>.

Changes in skeletal muscle metabolism, functioning, composition, and architecture have also been described and, in the last years, there has been mounting evidence that these changes play a pivotal role in the development of exercise intolerance and in the reduction of exercise capacity. Some clues point towards the existence of a peripheral reflex that becomes hyperactive secondary to the described skeletal muscle alterations and may contribute to the exercise intolerance and the early fatigability experienced by these patients <sup>5,6</sup>. Specifically, it has been reported that some hormonal systems (i.e. renin-angiotensin-aldosterone, vasopressin, and atrial natriuretic peptide) are over-activated and that patients show altered autonomic nervous system activity at rest and during exercise, with exaggerated sympathetic tone associated with parasympathetic withdrawal. While the exact mechanisms causing this hormonal and autonomic dysregulation are still to be fully elucidated, it appears that an exaggerated afferent feedback from group III/IV muscle afferents may be at least in part responsible for this dysregulation <sup>7,8,6,5</sup>. Importantly, physical inactivity appears to negatively affect the progression of the syndrome, while physical training can partially reverse this condition. Importantly, enhancements in exercise capacity observed after physical training appear to be the consequence of improvements in muscle and vascular function rather than in cardiac functions. Although effective in reducing mortality, classical pharmacological treatments, such as angiotensin-converting enzyme inhibitors,  $\beta$ -blockers, and diuretics show very limited or null effects on exercise capacity <sup>3,6,9-12</sup>.

To date, most of the literature investigating the role of group III/IV muscle afferents have focused on the physiology and pathophysiology of cardiovascular regulation during effort exercise. Only recently a series of experiments have emphasised their role on muscle fatigue development and in the inhibition of central motor drive, which negatively affect exercise performance<sup>13,14</sup>. Thus, overactivity of feedback from group III/IV muscle afferents may cause exercise intolerance with a double action: by inducing cardiovascular dysregulation and by facilitating the development of muscle fatigue. In the present narrative review, we will summarise the role of the group III/IV afferents feedback in the cardiovascular regulation during exercise and exercise-induced muscle fatigue of healthy people and their potential role in inducing exercise intolerance in CHF patients.

### **Role of group III and IV muscle afferents on the cardiovascular regulation during dynamic exercise in healthy subjects**

In healthy subjects, the cardiovascular adjustment to dynamic exercise is characterized by an increase in heart rate (HR) and stroke volume (SV), which together enhance CO. At the same time, a profound reduction in systemic vascular resistance (SVR) takes place due to metabolite-induced vasodilation in the working muscle. As result, mean arterial pressure (MAP) remains stable or slightly increases<sup>15-17</sup>. Behind these hemodynamic changes there is a fine tuning operated by neural mechanisms.

Specifically, at least three neural mechanisms concur in this physiological response. One is a central mechanism, commonly known as “central command”. In this mechanism, the cardiovascular control areas located in the brainstem are reflexively activated by regions of the brain responsible for motor unit recruitment. Central command is believed to establish a basal level of sympathetic activity and parasympathetic withdrawal to the cardiovascular apparatus closely linked to the exercise intensity<sup>18,19</sup>.

This basic pattern of autonomic activity is in turn modulated by a second mechanism arising from peripheral signals originating from type III/IV muscle afferents in the muscle, which act as mechano- and metabo- receptors. Group III/IV nerve endings represent more than 50% of the total muscle afferents and constitute the sensory arm of a reflex which is collectively termed



1  
2  
3  
4 the “exercise pressor reflex” (EPR). These muscle afferents convey information about the  
5 mechanical and metabolic variations of the contracting muscle via the spinal cord to the  
6 cardiovascular control centres within the brainstem<sup>18,20–22</sup>. It was reported that most group III  
7 afferents act mainly as “mechanoreceptors” as they respond to mechanical distortion, whereas  
8 group IV afferents appear to respond to metabolites accumulation, so that they can be considered  
9 as “metaboreceptors” as well as nociceptors. Several substances such as lactic acid, potassium,  
10 bradykinin, arachidonic acid products, ATP, diprotonated phosphate, and adenosine are thought to  
11 stimulate the metaboreceptors in the muscle<sup>23,24</sup>. It should be noticed that a sub-population of  
12 group III/IV nerve endings respond to both mechanical and chemical stimuli<sup>25,26</sup>. Some  
13 evidences suggest that mechanoreceptors can be sensitised by metabolites accumulation making  
14 it difficult to isolate their pure mechano- from metabo properties<sup>23,27</sup>. Group III/IV muscle  
15 afferents project to the dorsal horn of the spinal cord. However, little is known about the central  
16 pathways of the EPR their projections at cortical and subcortical level but it seems that the  
17 *medulla oblongata* is essential for its expression<sup>22,28,29</sup>.

18  
19 The activation of both central command and EPR leads to autonomic adjustments  
20 characterised by increase in sympathetic activity and parasympathetic withdrawal. This  
21 autonomic regulation is in turn modulated by the third reflex operating during exercise: the  
22 baroreflex. Arterial baroreceptors are located in the carotid sinus bifurcation and aortic arch and  
23 sense rapid changes in blood pressure thereby activating the baroreflex. When arterial blood  
24 pressure is acutely increased or reduced, the baroreceptors are stretched or compressed, and this  
25 deformation causes increment or reduction in afferent neuronal firing rate, respectively. The  
26 control over blood pressure is achieved by reflexively inducing rapid adjustments in HR and  
27 SVR in responses to changes in MAP<sup>30,31</sup>. The baroreflex activity avoids any excessive variation  
28 in blood pressure and opposes any mismatch between vascular resistance and CO<sup>32,32,33</sup>.

29  
30 One interesting point of the functioning of these reflexes is how they interact their  
31 interaction during dynamic exercise, as both the central command and the EPR can modulate the  
32 activity of the baroreflex<sup>34</sup>. In detail, it was reported that during exercise the operating point of  
33 the baroreflex is shifted and that the stimulus response curve is relocated to a higher arterial  
34 blood pressure in direct relation to exercise intensity, without any change in its sensitivity<sup>30,35,36</sup>.  
35 In short, the baroreflex is still operating during exercise, but the blood pressure operating point is  
36 higher than rest, although it is as effectively as at rest in controlling blood pressure<sup>30,34,37</sup>.

1  
2  
3  
4 It is remarkable that the target blood pressure can often be achieved despite a lack in  
5 response of one of the regulated variables, thereby suggesting that these reflexes operate with a  
6 high level of effectiveness and integration <sup>18,38,39</sup>. For example, it has been demonstrated in  
7 several human investigations dealing with EPR that when cardiac contractility cannot be  
8 enhanced, the possibility to increase SV and CO is precluded. Then, the target blood pressure is  
9 achieved by recruiting the SVR reserve (i.e., by inducing arteriolar vasoconstriction). Similarly,  
10 if venous return is impaired and/or the reserve in cardiac preload is exploited, then the  
11 recruitment of the SVR reserve is the main mechanism through which the EPR operates to adjust  
12 hemodynamics <sup>40</sup>. In short, it appears that whenever SV and CO can not properly increase (such  
13 as in CHF patients), then exaggerated arteriolar constriction becomes the main mechanism  
14 through which the target blood pressure is reached. Differently, in healthy subjects the preferred  
15 cardiovascular adjustment during EPR is a flow-mediated (i.e. CO-mediated) mechanism  
16 obtained by recruiting the inotropic and preload reserves <sup>40</sup>.

17 Hence, during exercise, central command, EPR, and baroreflex are all activated and  
18 complex interaction occurs between these reflexes. While it is well ascertained that some  
19 redundancy and neural occlusion exist between EPR and central command (i.e. their effects do  
20 not sum), it is also remarkable that they can modulate the activity of the other two. As previously  
21 exposed, the most studied interaction is the modulation of baroreflex operated by central  
22 command and EPR. However, interaction has also been demonstrated between central command  
23 and EPR. Actually, several evidences suggest that inputs from type III/IV muscle afferences  
24 modulate the central command activity and exert an inhibitory effect on central motor drive <sup>41</sup>. In  
25 particular, it was observed that reduction in afferent input from type III/IV muscle afferents  
26 during exercise obtained with epidural anaesthesia resulted in an increase in central command  
27 activity. These findings support the thesis that central command cannot work properly without  
28 adequate feedback from peripheral muscle and that, at the same time, this feedback limits central  
29 command and motor drive <sup>13,41</sup>.

### 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 **Role of group III and IV muscle afferents on the development of muscle fatigue during** 56 **dynamic exercise in healthy subjects** 57 58 59 60 61 62 63 64 65

1  
2  
3  
4 Sustained physical exercise inexorably leads to a reduced capacity to generate maximal  
5 force or power. This has been commonly described as muscle fatigue <sup>14</sup>. Most of muscle fatigue  
6 has been documented to occur at or distal to the neuromuscular junction <sup>42</sup>, and has been  
7 commonly defined peripheral fatigue. Conversely, central fatigue refers to the inability of the  
8 central nervous system to optimally recruit the muscle (e.g. a significant decrease in voluntary  
9 activation) <sup>14</sup>. Supraspinal fatigue, a subset of central fatigue, can be described as a suboptimal  
10 output from the motor cortex <sup>14</sup>. Consequently, the interaction between central and peripheral  
11 fatigue leads to decrease in maximal force or power. The role and interplay of central and  
12 peripheral fatigue in exercise tolerance and termination has been object of discussion for several  
13 years <sup>43,44</sup>. Peripheral fatigue is measured by comparing the force of the muscle elicited by  
14 electrical stimulation of the corresponding motor nerve before and after exercise <sup>45</sup>.  
15 Quantification of central fatigue is generally performed with the superimposed twitch technique  
16 <sup>46</sup>. More recently, transcranial magnetic stimulation (TMS) has been effectively used to study and  
17 quantify supraspinal fatigue on different exercise paradigms <sup>47</sup>.

18  
19 Several experiments have been performed to understand and identify the physiological  
20 mechanisms contributing to the generation of muscle fatigue <sup>14,43</sup>. A considerable amount of  
21 experimental evidences supports the hypothesis that during high intensity exercise, the activity of  
22 group III/IV muscle afferents might facilitate the development of central fatigue via an inhibitory  
23 feedback at different sites of the motor pathway and also by influencing the level of motor unit  
24 activation <sup>41,48</sup>. Injection of hypertonic saline in the muscle has been classically used as  
25 experimental approach to stimulate type III/IV muscle afferents. A reduction of low-threshold  
26 motor unit discharge rate during low intensity muscular contraction <sup>49,50</sup> and maximal force  
27 production of knee extensor <sup>50</sup> and elbow flexors muscles <sup>51</sup> have been found this approach.  
28 Other studies reported a decrease in motor evoked potentials elicited by transcranial direct  
29 stimulation TMS, thus providing evidences of an inhibitory effect at supraspinal level <sup>52</sup>. The  
30 reduction in maximal force production seems to be caused by decrease in voluntary activation  
31 (e.g. increase in central fatigue). This hypothesis seems to be confirmed in studies where  
32 voluntary activation was significantly reduced in elbow flexors muscles <sup>51</sup>. On the other hand,  
33 other studies reported an increase in spinal motoneurons excitability <sup>53</sup>. Overall, these studies  
34 showed that motor unit activation can be partially regulated by peripheral reflexes elicited by  
35 group III/IV muscle afferents.

Post-exercise circulatory occlusion has also been employed as alternative experimental approach to stimulate group III/IV muscle afferents. In regards, early investigations demonstrated that maximal voluntary contraction and voluntary activation were significantly reduced and did not recover until the circulation was restored<sup>54-57</sup>. Interestingly, when the fatigued muscle was kept ischemic, the decline in maximal force and voluntary activation was also present in unfatigued muscle of the same limb<sup>55,56</sup>. These findings suggest the presence of convergence and divergence effect at spinal level<sup>58</sup>, where muscle afferents from one muscle may have projections to the dorsal horn receiving inputs from other adjacent muscles. Studies involving TMS demonstrated that the decline maximal force production and voluntary activation was also caused by an inhibitory effect at supraspinal level<sup>55,56,59</sup>.

Pharmacological blockade has also been adopted as experimental approach to study the role of group III/IV muscle afferents<sup>41</sup>. This type of intervention performed prior whole-body exercise, is able to attenuate approximately 60% of feedback from these afferents. Overall, these investigations reported that during high intensity cycling exercise, voluntary drive (estimated by means of electromyography), metabolites accumulation, and peripheral fatigue increased when the feedback from exercising muscles was attenuated<sup>60-62</sup>. It should be considered, that in these studies, physical performance was unchanged or impaired when afferent feedback was attenuated, and this was probably the consequence of an impaired cardiorespiratory response<sup>41,61,63</sup>. More recently, a series of experiments involving TMS reported an increase in corticospinal excitability when feedback from exercising muscles was attenuated<sup>64-66</sup>. These preliminary findings seem to confirm previous experiments showing that group III/IV muscle afferents promote central fatigue during exercise.

### **Group III and IV muscle afferents and their role in cardiovascular regulation and fatigability in patients with chronic heart failure**

During EPR, several abnormalities in the cardiovascular regulation have been demonstrated in individuals suffering from CHF. To study the metaboreflex, i.e. the metabolic part of the EPR, some human studies employed the post-exercise muscle ischemia method, which induces metabolites accumulation thereby stimulating type III/IV muscle afferents in the

1  
2  
3  
4 muscle. During the metaboreflex activation in patients with CHF, an increase in MAP similar to  
5 that observed in healthy individuals was found. However, the mechanisms underlying this  
6 cardiovascular response were markedly different between patients and controls. In detail, in  
7 patients suffering from CHF the rise in MAP was reached via a SVR increase, while in healthy  
8 individuals this was the result of a flow increment, i.e. CO elevation <sup>67</sup>. This observation was  
9 recently replicated also in patients suffering from heart failure with preserved ejection fraction <sup>68</sup> as  
10 well as in patients with coronary artery disease <sup>69</sup>. This abnormal hemodynamics seemed the  
11 consequence of the incapacity of CHF patients to recruit the reserves in cardiac performance and  
12 in cardiac pre-load in response to the metaboreflex. The exaggerated increase in SVR (i.e.  
13 arteriolar constriction) compensated for the inability to increase SV. Interesting, in CHF patients  
14 the MAP response was well preserved notwithstanding their lower CO in comparison with  
15 healthy subjects. Hence, it appears that CHF causes a functional shift from a flow-mediated (i.e.  
16 CO increase) to a vasoconstriction-mediated (i.e. SVR increase) in the mechanisms by which the  
17 target blood pressure is reached during EPR. It is to be considered that this hemodynamic  
18 scenario closely resembles what has been also reported in animal models of CHF <sup>70-72</sup>.

19  
20 It is to be highlighted that the described exaggerated arteriolar constriction in response to  
21 metaboreflex potentially restrains muscle perfusion <sup>73</sup>, and this likely contributes to the early  
22 development of fatigue and exercise intolerance shown by CHF patients. In detail, while in  
23 healthy subjects metaboreflex activation maintains skeletal muscle perfusion <sup>73</sup>, this is not the  
24 case in CHF, where exaggerated vasoconstriction takes place during the metaboreflex. In this  
25 scenario, even the exercising muscle may become vasoconstricted <sup>67,74,75</sup> and this occurrence  
26 may lead to deleterious consequences in terms of exercise tolerance and muscle tropism.

27  
28 It has been proposed the so called “muscle hypothesis” to explain at least in part the  
29 exercise intolerance shown by CHF patients. In detail, it has been suggested that CHF initiates a  
30 vicious circle where damage to the heart and disturbance in central haemodynamics trigger  
31 compensatory mechanisms, including neurohumoral and sympathetic activation, which  
32 persistently vasoconstricts the muscle circulation. In the longer term, this condition becomes  
33 harmful and damages at vascular and endothelial level develop, with chronic inflammation, and  
34 necrosis at muscular level. Various signs of myopathy, muscle mass reduction, and abnormal  
35 metabolic and mechanical functions are actually present in CHF <sup>76,77</sup>. Importantly, these muscle  
36 abnormalities correlate better with exercise tolerance compared to measures of left ventricular  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

function<sup>74</sup>. The described muscle abnormalities in turn cause elevation in the feedback from III/IV afferents during muscle contraction, and this heightens EPR activity and dys-regulates hemodynamics, with excessive arteriolar constriction and muscle hypoperfusion. In short, in CHF central hemodynamic abnormalities in response to EPR initiates a vicious circle which, in the longer term, causes muscle hypoperfusion, muscle wasting, and reduction in strength<sup>5,78</sup>.

In support to the “muscle hypothesis” there are experimental findings in heart transplant recipients during the metaboreflex activation. In these patients exercise capacity, although improved, remains abnormally impaired after transplant compared to normal individuals. This indicates that restoring cardiac function does not fully enhance aerobic metabolism. A possible explanation for the incomplete recovery might be muscular abnormalities which developed before transplant and persist after transplant, thereby impairing exercise capacity in these patients<sup>79,80</sup>. Moreover, it has been observed that improvement in exercise capacity after heart transplant was paralleled by improvements in cardiovascular response to metaboreflex, with a gradual reduction in the metaboreflex-induced arteriolar constriction<sup>79</sup>. Collectively, these findings in heart transplant recipients seem to indicate that the EPR is dys-regulated in these patients before transplant and that this dys-regulation tends to ameliorate several months after transplant, in parallel with muscle metabolism and functions. This observation appears to be in line with the “muscle hypothesis” of CHF.

Some authors have argued against the concept that metaboreflex is accentuated in the CHF syndrome. Specifically, they have proposed that mechanoreceptor rather than metaboreceptor stimulation is responsible for the abnormal haemodynamic observed in CHF during EPR activation<sup>81-83</sup>. It has also been proposed that metaboreflex control of sympathetic activity is attenuated in CHF and that metaboreceptors are desensitised in this syndrome<sup>28</sup>. It is likely that the conflicting results in scientific literature on whether muscle metaboreflex is attenuated or accentuated may depend on the degree of muscle abnormalities of the CHF population, the degree of metaboreceptor desensitisation, and the mode of exercise being performed. Furthermore, authors reporting attenuated metaboreflex and accentuated mechanoreflex employed animal model of CHF (mainly rats), thus the application of these findings in humans is contentious. Moreover, evidence suggests that mechanoreceptors are sensitised by metabolites, thus rendering it difficult to differentiate the role of mechanoreflex from that of metaboreflex<sup>27</sup>. Finally, it should be considered that, in the human model, most

1  
2  
3  
4 studies dealing with metaboreflex employed the post-exercise muscle ischemia method to assess  
5 metaboreflex function. This manoeuvre probably rules out any contribution of mechanoreceptors  
6 since they do not operate in this setting.  
7  
8

9  
10 Whatever the mechanoreflex or the metaboreflex are responsible for the abnormal  
11 elevation in EPR activity, the EPR is dysfunctional in these patients. It is interesting to note that  
12 Amann and colleagues <sup>84</sup> were able to demonstrate that lumbar intrathecal fentanyl reduced the  
13 excessive vascular resistance during knee-extensor exercise in a CHF population, thereby  
14 demonstrating a role of type III/IV muscle afferents in the abnormal hemodynamics in this  
15 syndrome. More recently, Van Iterson and colleagues <sup>85</sup> reported that blocking type III/IV muscle  
16 afferents with intrathecal fentanyl in a population of CHF patients resulted in a faster  $\dot{V}O_2$   
17 kinetics. They hypothesised that the slower  $\dot{V}O_2$  kinetics of CHF was the consequence of  
18 peripheral and central hemodynamic maldistribution due to abnormal group III/IV muscle  
19 afferents activation and that blocking these afferents could at least partially restore a normal  
20 exercise response.  
21  
22

23  
24 Concerning the role played by type III/IV muscle afferents on exercise capacity, it should  
25 be underscored that very few studies have been conducted in clinical population <sup>84,86</sup>. Gagnon  
26 and colleagues <sup>86</sup> were the first to investigate the exercise response following their  
27 pharmacological blockade in COPD. Contrarily to what found in healthy population, endurance  
28 time during a cycling constant work-rate was enhanced by an average of 215 seconds. According  
29 to the authors, the reduced and delayed hyper-ventilatory response and lowered perceived  
30 dyspnoea during exercise might provide a possible explanation for the increased exercise  
31 capacity. Furthermore, a deeper loss in quadriceps muscle strength and a higher lactate level after  
32 exercise with spinal anaesthesia was also found. In CHF patients, Amann and colleagues <sup>84</sup> found  
33 an increase in vascular conductance, peripheral blood flow (15% increase), and leg oxygen  
34 delivery together with a significant reduction in MAP following intrathecal fentanyl.  
35 Interestingly, the decline in maximal force production of the quadriceps following exercise was  
36 attenuated by 30% compared to control condition. Taken together, these findings suggest that in  
37 these kinds of clinical population, type III/IV afferents feedback might play a pivotal role to  
38 reduce exercise tolerance <sup>6,87,88</sup>.  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56

57 One phenomenon recently proposed to explain the potential influence of group III/IV  
58 afferents on the muscle fatigue development is their ability to affect cerebral blood flow and  
59  
60  
61  
62  
63  
64  
65

oxygenation. It has been proposed that the EPR activation lowered cerebral perfusion by counteracting the normal vasodilation occurring at brain level during exercise. This would increase the sense of effort and impair motor drive <sup>9</sup>. However, the regulation of cerebral circulation is complex, and more research is warranted to better understand the phenomenon and to confirm this hypothesis.

Experimental studies proposed that afferent feedback from ventilatory muscles might be important for exercise intolerance in CHF patients. Both animal and human model reported histological and biochemical alterations of the diaphragm muscle in CHF <sup>89</sup>. Respiratory muscle dysfunction is typically observed in CHF patients and this is often called as respiratory muscle weakness which is caused by a substantial reduction in respiratory muscle strength (in particularly the diaphragm) <sup>90</sup>. During exercise, CHF patients develop early diaphragmatic fatigue by therefore limiting the ventilatory response and so reducing pulmonary gas exchange and oxygen delivery. Furthermore, increased in breathlessness, exertional dyspnoea from low exercise intensities is typically observed. Similarly, to the locomotor muscles, an exaggerated metaboreflex from respiratory muscle has been observed <sup>91</sup>. This mechanism, also described as inspiratory muscle metaboreflex, is particularly important during sustained exercise as it modulates the competition for blood flow between the locomotor and respiratory muscles <sup>92</sup>. This mismatch potentially leads to increase in the ventilatory work and may exacerbate exertional dyspnoea and exercise intolerance. Taken together, these respiratory muscle abnormalities have been shown to contribute to early development of fatigue in CHF patients <sup>90</sup>.

It should be considered that the number of studies is very limited and therefore the precise role of group III/IV muscle afferents contributing to the development of muscle fatigue and exercise tolerance in the clinical population is largely unknown. Nevertheless, these preliminary studies provide encouraging evidences that these muscle afferents can be the target of future therapeutic strategies. The major putative mechanisms responsible for the exercise intolerance and early fatigue induced by type III/IV afferents feedback in CHF are shown in Fig 1.

### **Exercise training as therapy for chronic heart failure patients**



1  
2  
3  
4 Aerobic exercise training is recognized as an important adjunct for improving the quality  
5 of life of CHF patients. The benefits aerobic training have been discussed in previous reviews  
6  
7  
8<sup>93,94</sup>. Aerobic training demonstrated to positively affect maximal oxygen consumption, central  
9 and peripheral hemodynamic function, peripheral vascular function and muscular function.  
10 These adaptations result in a higher workload for the same HR and perceived exertion<sup>93</sup>.  
11 Continuous aerobic training of 45-60 min duration is well tolerated and recommended for CHF  
12 patients. Recently, interval/intermittent aerobic training has been shown to be more effective.  
13 This involves <5 min bouts at 90-95% of the maximal exercise capacity interspaced by >3 min  
14 of recovery<sup>94</sup>.  
15

16  
17 Resistance training has also been introduced to counteract the decline in functional  
18 alteration and muscle mass of the locomotor muscles. Previous works recommended an intensity  
19 of 30-40% of 1RM and RPE <12 for increasing local aerobic capacity, while 40-60% of 1RM  
20 and RPE <15 for increasing muscle mass. It is importance to notify that aerobic exercise remain  
21 the main training and therefore the resistance training can be considered as complement<sup>94</sup>.  
22

23  
24 Since respiratory muscle weakness is inversely correlated with exercise capacity,  
25 interventions with the potential to improve respiratory muscle strength might be able to counter  
26 this condition. Recent studies focused on the role of respiratory muscle training for the  
27 improvement of respiratory muscle strength in CHF. Several beneficial effects such as  
28 improvement in maximal inspiratory capacity, improvement in peripheral and respiratory oxygen  
29 supply, reduction in exertional dyspnoea have been reported together with improved exercise  
30 capacity and exercise tolerance with a better quality of life<sup>98</sup>. Winkelmann et al.<sup>99</sup> showed that  
31 inspiratory muscle training combined with aerobic training was more beneficial than aerobic  
32 training alone in CHF patients. However, the optimal training regimen is yet to be defined.  
33 However, it seems that the benefits of respiratory muscle training appear to be intensity-  
34 dependent suggesting that high intensity training regimens is required to obtain improvement in  
35 aerobic capacity<sup>100</sup>. Interestingly, a study performed by Chiappa and colleagues<sup>91</sup> showed that  
36 inspiratory muscle training was capable to decrease limb vasculature resistance by increasing  
37 blood flow of limb muscles at rest and during exercise. One of the main results of this  
38 adaptations was the attenuation of the metaboreflex activity<sup>91</sup>. Other mechanisms might also be  
39 responsible for the increase in exercise capacity in CHF patients such as resting left ventricular  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

function, endothelial vasodilator function and improved ventilatory response. However, other mechanisms are yet to be elucidated.

In animal models of CHF (rats), it was demonstrated that exercise exerts beneficial effects on the exaggerated EPR, although the underlying mechanisms have not be completely elucidated <sup>95,96</sup>. Observations in humans reported that exercise training could reverse the exaggerated exercise-induced sympathetic activity, vasoconstriction, and ventilatory drive in patients with CHF <sup>97</sup>. More recently, these observations have been confirmed and support the concept that the exaggerated EPR activity is at least in part responsible for the sympathetic overactivity in CHF patients and that this condition can be successfully counteracted by exercise training <sup>95</sup>. However, it is to be acknowledged that the mechanisms of exercise-mediated beneficial effects on EPR remain largely unknown in humans. Further studies are warranted to definitively prove whether exercise training is effective in reducing the exaggerated EPR in these patients.

## Conclusions and future directions

In summary, the pathophysiological mechanisms of exercise intolerance and exercise induced muscle fatigue in patients with CHF are complex and involve peripheral and central factors. In this context, reflexes mediated by group III/IV muscle afferents appear to play an important role in the phenomenon. The exaggerated afferent feedback coming from these fibres potentially causes hemodynamic dysregulation, with excessive sympatho-excitation and arteriolar constriction. The abnormally elevated neural feedback may also exacerbate the rate of development of peripheral and central fatigue by causing a restriction in motoneuronal output. Whether this exaggerated feedback arises from the activity of mechano- or metabo-receptors is still a matter of debate. There is also the possibility that both receptors are involved in the phenomenon. Future study specifically designed is necessary to unravel this question.

Although demonstrated in few studies, exercise induced muscle fatigue in clinical population can be partially attributed to a higher and/or abnormal activity of group III/IV muscle afferents and also explain the reduced exercise capacity and exercise intolerance of patients suffering from CHF. In light of these findings, further studies are required to elucidate the

mechanisms of group III/IV muscle afferents at various sites of the motor pathway and peripheral level during exercise.

It is important that future investigations take into account the possible effects of pharmacological therapy on the correction of the type III/IV muscle afferents hyperactivity. From a clinical perspective it would be useful to verify whether blockade these receptors limits the excessive sympathetic excitation and the reduced motor output observed in CHF patients. To the best of our knowledge, a drug that specifically blocks these afferents has yet to be tested in humans. Another further field for future research is the effect of physical training on type III/IV afferents activity. Such an investigation would reveal whether a physical training program would dampen the hyperactivity shown by these muscle afferents in CHF syndrome. This would have the practical consequence to test whether the prescription of physical activity and the adoption of an active lifestyle is an effective means to treat the exercise intolerance and to reduce fatigability in these patients.

#### **Author contribution**

LA and AC contributed to the conception or design of the work. LA and AC drafted and critically revised the manuscript. LA and AC gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

#### **Funding Acknowledgements**

The authors received no financial support for the research, authorship, and/or publication of this article.

#### **Conflict of interest**

Luca Angius and Antonio Crisafulli declare that they have no conflicts of interest relevant to the content of this review.

## References

1. Braunwald E. Heart failure. *JACC Heart Fail* 2013; 1: 1–20.
2. Del Buono MG, Arena R, Borlaug BA, et al. Exercise Intolerance in Patients With Heart Failure: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2019; 73: 2209–2225.
3. Haykowsky MJ, Timmons MP, Kruger C, et al. Meta-analysis of aerobic interval training on exercise capacity and systolic function in patients with heart failure and reduced ejection fractions. *Am J Cardiol* 2013; 111: 1466–1469.
4. Haykowsky MJ, Tomczak CR, Scott JM, et al. Determinants of exercise intolerance in patients with heart failure and reduced or preserved ejection fraction. *J Appl Physiol Bethesda Md 1985* 2015; 119: 739–744.
5. Piepoli MF, Crisafulli A. Pathophysiology of human heart failure: importance of skeletal muscle myopathy and reflexes. *Exp Physiol* 2014; 99: 609–615.
6. Piepoli MF, Kaczmarek A, Francis DP, et al. Reduced peripheral skeletal muscle mass and abnormal reflex physiology in chronic heart failure. *Circulation* 2006; 114: 126–134.
7. Amann M, Sidhu SK, Weavil JC, et al. Autonomic responses to exercise: group III/IV muscle afferents and fatigue. *Auton Neurosci Basic Clin* 2015; 188: 19–23.
8. Floras JS. Clinical aspects of sympathetic activation and parasympathetic withdrawal in heart failure. *J Am Coll Cardiol* 1993; 22: 72A–84A.
9. Brassard P, Gustafsson F. Exercise Intolerance in Heart Failure: Did We Forget the Brain? *Can J Cardiol* 2016; 32: 475–484.
10. Bhambhani YN. Muscle oxygenation trends during dynamic exercise measured by near infrared spectroscopy. *Can J Appl Physiol Rev Can Physiol Appl* 2004; 29: 504–523.
11. Jónsdóttir S, Andersen KK, Sigurosson AF, et al. The effect of physical training in chronic heart failure. *Eur J Heart Fail* 2006; 8: 97–101.
12. Wang H-J, Li Y-L, Zucker IH, et al. Exercise training prevents skeletal muscle afferent sensitization in rats with chronic heart failure. *Am J Physiol Regul Integr Comp Physiol* 2012; 302: R1260–1270.
13. Amann M, Calbet JAL. Convective oxygen transport and fatigue. *J Appl Physiol* 2008; 104: 861–870.
14. Gandevia SC. Spinal and supraspinal factors in human muscle fatigue. *Physiol Rev* 2001; 81: 1725–1789.

15. Crisafulli A, Salis E, Pittau G, et al. Modulation of cardiac contractility by muscle metaboreflex following efforts of different intensities in humans. *Am J Physiol Heart Circ Physiol* 2006; 291: H3035-3042.
16. Higginbotham MB, Morris KG, Williams RS, et al. Regulation of stroke volume during submaximal and maximal upright exercise in normal man. *Circ Res* 1986; 58: 281–291.
17. Lewis SF, Taylor WF, Graham RM, et al. Cardiovascular responses to exercise as functions of absolute and relative work load. *J Appl Physiol* 1983; 54: 1314–1323.
18. Nobrega ACL, O’Leary D, Silva BM, et al. Neural regulation of cardiovascular response to exercise: role of central command and peripheral afferents. *BioMed Res Int* 2014; 2014: 478965.
19. Seals DR. Influence of muscle mass on sympathetic neural activation during isometric exercise. *J Appl Physiol Bethesda Md* 1985 1989; 67: 1801–1806.
20. Laurin J, Pertici V, Dousset E, et al. Group III and IV muscle afferents: role on central motor drive and clinical implications. *Neuroscience* 2015; 290: 543–551.
21. McCloskey DI. Kinesthetic sensibility. *Physiol Rev* 1978; 58: 763–820.
22. Rowell LB, O’Leary DS. Reflex control of the circulation during exercise: chemoreflexes and mechanoreflexes. *J Appl Physiol Bethesda Md* 1985 1990; 69: 407–418.
23. Adreani CM, Hill JM, Kaufman MP. Responses of group III and IV muscle afferents to dynamic exercise. *J Appl Physiol Bethesda Md* 1985 1997; 82: 1811–1817.
24. Kniffki KD, Mense S, Schmidt RF. Responses of group IV afferent units from skeletal muscle to stretch, contraction and chemical stimulation. *Exp Brain Res* 1978; 31: 511–522.
25. Kaufman MP, Longhurst JC, Rybicki KJ, et al. Effects of static muscular contraction on impulse activity of groups III and IV afferents in cats. *J Appl Physiol* 1983; 55: 105–112.
26. Matsukawa K, Wall PT, Wilson LB, et al. Reflex stimulation of cardiac sympathetic nerve activity during static muscle contraction in cats. *Am J Physiol* 1994; 267: H821-827.
27. Murphy MN, Mizuno M, Mitchell JH, et al. Cardiovascular regulation by skeletal muscle reflexes in health and disease. *Am J Physiol Heart Circ Physiol* 2011; 301: H1191-1204.
28. Sinoway LI, Li J. A perspective on the muscle reflex: implications for congestive heart failure. *J Appl Physiol Bethesda Md* 1985 2005; 99: 5–22.
29. Kaufman MP, Rybicki KJ. Discharge properties of group III and IV muscle afferents: their responses to mechanical and metabolic stimuli. *Circ Res* 1987; 61: I60-65.
30. Crisafulli A, Marongiu E, Ogoh S. Cardiovascular Reflexes Activity and Their Interaction during Exercise. *BioMed Res Int* 2015; 2015: 394183.

31. Fadel PJ, Raven PB. Human investigations into the arterial and cardiopulmonary baroreflexes during exercise. *Exp Physiol* 2012; 97: 39–50.
32. Iellamo F, Legramante JM, Raimondi G, et al. Baroreflex control of sinus node during dynamic exercise in humans: effects of central command and muscle reflexes. *Am J Physiol* 1997; 272: H1157-1164.
33. O’Leary DS. Autonomic mechanisms of muscle metaboreflex control of heart rate. *J Appl Physiol Bethesda Md* 1985 1993; 74: 1748–1754.
34. Raven PB, Fadel PJ, Ogoh S. Arterial baroreflex resetting during exercise: a current perspective. *Exp Physiol* 2006; 91: 37–49.
35. Fadel PJ, Ogoh S, Keller DM, et al. Recent insights into carotid baroreflex function in humans using the variable pressure neck chamber. *Exp Physiol* 2003; 88: 671–680.
36. Norton KH, Boushel R, Strange S, et al. Resetting of the carotid arterial baroreflex during dynamic exercise in humans. *J Appl Physiol Bethesda Md* 1985 1999; 87: 332–338.
37. Raven PB, Potts JT, Shi X. Baroreflex regulation of blood pressure during dynamic exercise. *Exerc Sport Sci Rev* 1997; 25: 365–389.
38. Crisafulli A, Melis F, Lai AC, et al. Haemodynamics during a complete exercise induced atrioventricular block. *Br J Sports Med* 2002; 36: 69–70.
39. Rowland TW. Circulatory responses to exercise: are we misreading Fick? *Chest* 2005; 127: 1023–1030.
40. Crisafulli A. The Impact of Cardiovascular Diseases on Cardiovascular Regulation During Exercise in Humans: Studies on Metaboreflex Activation Elicited by the Post-exercise Muscle Ischemia Method. *Curr Cardiol Rev* 2017; 13: 293–300.
41. Amann M. Central and peripheral fatigue: interaction during cycling exercise in humans. *Med Sci Sports Exerc* 2011; 43: 2039–2045.
42. Allen DG, Lamb GD, Westerblad H. Skeletal Muscle Fatigue: Cellular Mechanisms. *Physiol Rev* 2008; 88: 287–332.
43. Enoka RM, Duchateau J. Translating Fatigue to Human Performance. *Med Sci Sports Exerc* 2016; 48: 2228–2238.
44. Hureau TJ, Romer LM, Amann M. The ‘sensory tolerance limit’: A hypothetical construct determining exercise performance? *Eur J Sport Sci* 2018; 18: 13–24.
45. Place N, Maffiuletti NA, Martin A, et al. Assessment of the reliability of central and peripheral fatigue after sustained maximal voluntary contraction of the quadriceps muscle. *Muscle Nerve* 2007; 35: 486–495.

46. Merton PA. Voluntary strength and fatigue. *J Physiol* 1954; 123: 553–564.
47. Sidhu SK, Bentley DJ, Carroll TJ. Cortical voluntary activation of the human knee extensors can be reliably estimated using transcranial magnetic stimulation. *Muscle Nerve* 2009; 39: 186–196.
48. Taylor JL, Amann M, Duchateau J, et al. Neural Contributions to Muscle Fatigue: From the Brain to the Muscle and Back Again. *Med Sci Sports Exerc* 2016; 48: 2294–2306.
49. Farina D, Arendt-Nielsen L, Graven-Nielsen T. Experimental muscle pain reduces initial motor unit discharge rates during sustained submaximal contractions. *J Appl Physiol Bethesda Md* 1985 2005; 98: 999–1005.
50. Graven-Nielsen T, Arendt-Nielsen L, Mense S. Thermosensitivity of muscle: high-intensity thermal stimulation of muscle tissue induces muscle pain in humans. *J Physiol* 2002; 540: 647–656.
51. Khan SI, McNeil CJ, Gandevia SC, et al. Effect of experimental muscle pain on maximal voluntary activation of human biceps brachii muscle. *J Appl Physiol Bethesda Md* 1985 2011; 111: 743–750.
52. Le Pera D, Graven-Nielsen T, Valeriani M, et al. Inhibition of motor system excitability at cortical and spinal level by tonic muscle pain. *Clin Neurophysiol Off J Int Fed Clin Neurophysiol* 2001; 112: 1633–1641.
53. Martin PG, Weerakkody N, Gandevia SC, et al. Group III and IV muscle afferents differentially affect the motor cortex and motoneurons in humans: Changes in the motor pathways with intramuscular hypertonic saline. *J Physiol* 2008; 586: 1277–1289.
54. Gandevia SC, Allen GM, Butler JE, et al. Supraspinal factors in human muscle fatigue: evidence for suboptimal output from the motor cortex. *J Physiol* 1996; 490: 529–536.
55. Kennedy DS, McNeil CJ, Gandevia SC, et al. Firing of antagonist small-diameter muscle afferents reduces voluntary activation and torque of elbow flexors: Small-diameter afferents reduce voluntary drive to elbow flexors. *J Physiol* 2013; 591: 3591–3604.
56. Kennedy DS, McNeil CJ, Gandevia SC, et al. Fatigue-related firing of distal muscle nociceptors reduces voluntary activation of proximal muscles of the same limb. *J Appl Physiol Bethesda Md* 1985 2014; 116: 385–394.
57. Kennedy DS, Fitzpatrick SC, Gandevia SC, et al. Fatigue-related firing of muscle nociceptors reduces voluntary activation of ipsilateral but not contralateral lower limb muscles. *J Appl Physiol Bethesda Md* 1985 2015; 118: 408–418.
58. Schaible H-G, Schmidt RF, Willis WD. Convergent inputs from articular, cutaneous and muscle receptors onto ascending tract cells in the cat spinal cord. *Exp Brain Res* 1987; 66: 479–488.

59. Pageaux B, Angius L, Hopker JG, et al. Central alterations of neuromuscular function and feedback from group III-IV muscle afferents following exhaustive high-intensity one-leg dynamic exercise. *Am J Physiol Regul Integr Comp Physiol* 2015; 308: R1008-1020.
60. Amann M, Proctor LT, Sebranek JJ, et al. Opioid-mediated muscle afferents inhibit central motor drive and limit peripheral muscle fatigue development in humans. *J Physiol* 2009; 587: 271–283.
61. Amann M, Blain GM, Proctor LT, et al. Implications of group III and IV muscle afferents for high-intensity endurance exercise performance in humans. *J Physiol* 2011; 589: 5299–5309.
62. Blain GM, Mangum TS, Sidhu SK, et al. Group III/IV muscle afferents limit the intramuscular metabolic perturbation during whole body exercise in humans. *J Physiol* 2016; 594: 5303–5315.
63. Smith SA, Querry RG, Fadel PJ, et al. Partial blockade of skeletal muscle somatosensory afferents attenuates baroreflex resetting during exercise in humans. *J Physiol* 2003; 551: 1013–1021.
64. Sidhu SK, Weavil JC, Mangum TS, et al. Group III/IV locomotor muscle afferents alter motor cortical and corticospinal excitability and promote central fatigue during cycling exercise. *Clin Neurophysiol Off J Int Fed Clin Neurophysiol* 2017; 128: 44–55.
65. Sidhu SK, Weavil JC, Thurston TS, et al. Fatigue-related group III/IV muscle afferent feedback facilitates intracortical inhibition during locomotor exercise. *J Physiol* 2018; 596: 4789–4801.
66. Sidhu SK, Weavil JC, Venturelli M, et al. Spinal  $\mu$ -opioid receptor-sensitive lower limb muscle afferents determine corticospinal responsiveness and promote central fatigue in upper limb muscle. *J Physiol* 2014; 592: 5011–5024.
67. Crisafulli A, Salis E, Tocco F, et al. Impaired central hemodynamic response and exaggerated vasoconstriction during muscle metaboreflex activation in heart failure patients. *Am J Physiol-Heart Circ Physiol* 2007; 292: H2988–H2996.
68. Roberto S, Mulliri G, Milia R, et al. Hemodynamic response to muscle reflex is abnormal in patients with heart failure with preserved ejection fraction. *J Appl Physiol Bethesda Md* 1985 2017; 122: 376–385.
69. Magnani S, Roberto S, Sainas G, et al. Metaboreflex-mediated hemodynamic abnormalities in individuals with coronary artery disease without overt signs or symptoms of heart failure. *Am J Physiol Heart Circ Physiol* 2018; 314: H452–H463.
70. O’Leary DS, Senador D, Augustyniak RA. Muscle metaboreflex-induced central blood volume mobilization in heart failure. *Am J Physiol Heart Circ Physiol* 2019; 316: H1047–H1052.



- 1
- 2
- 3
- 4 71. O'Leary DS. Altered reflex cardiovascular control during exercise in heart failure: animal
- 5 studies. *Exp Physiol* 2006; 91: 73–77.
- 6
- 7
- 8 72. Kaur J, Senador D, Krishnan AC, et al. Muscle metaboreflex-induced vasoconstriction in
- 9 the ischemic active muscle is exaggerated in heart failure. *Am J Physiol Heart Circ Physiol*
- 10 2018; 314: H11–H18.
- 11
- 12 73. Shoemaker JK, Naylor HL, Hogeman CS, et al. Blood flow dynamics in heart failure.
- 13 *Circulation* 1999; 99: 3002–3008.
- 14
- 15
- 16 74. Piepoli MF, Dimopoulos K, Concu A, et al. Cardiovascular and ventilatory control during
- 17 exercise in chronic heart failure: role of muscle reflexes. *Int J Cardiol* 2008; 130: 3–10.
- 18
- 19 75. Ponikowski PP, Chua TP, Francis DP, et al. Muscle ergoreceptor overactivity reflects
- 20 deterioration in clinical status and cardiorespiratory reflex control in chronic heart failure.
- 21 *Circulation* 2001; 104: 2324–2330.
- 22
- 23
- 24 76. Anker SD, Ponikowski P, Varney S, et al. Wasting as independent risk factor for mortality
- 25 in chronic heart failure. *Lancet Lond Engl* 1997; 349: 1050–1053.
- 26
- 27 77. Massie BM, Simonini A, Sahgal P, et al. Relation of systemic and local muscle exercise
- 28 capacity to skeletal muscle characteristics in men with congestive heart failure. *J Am Coll*
- 29 *Cardiol* 1996; 27: 140–145.
- 30
- 31
- 32 78. Coats AJ, Clark AL, Piepoli M, et al. Symptoms and quality of life in heart failure: the
- 33 muscle hypothesis. *Br Heart J* 1994; 72: S36–39.
- 34
- 35
- 36 79. Crisafulli A, Tocco F, Milia R, et al. Progressive improvement in hemodynamic response to
- 37 muscle metaboreflex in heart transplant recipients. *J Appl Physiol Bethesda Md* 1985 2013;
- 38 114: 421–427.
- 39
- 40 80. Houssiere A, Gujic M, Deboeck G, et al. Increased metaboreflex activity is related to
- 41 exercise intolerance in heart transplant patients. *Am J Physiol Heart Circ Physiol* 2007;
- 42 293: H3699–3706.
- 43
- 44
- 45 81. Middlekauff HR, Sinoway LI. Increased mechanoreceptor stimulation explains the
- 46 exaggerated exercise pressor reflex seen in heart failure. *J Appl Physiol Bethesda Md* 1985
- 47 2007; 102: 492–494; discussion 496.
- 48
- 49
- 50 82. Smith SA, Mitchell JH, Naseem RH, et al. Mechanoreflex mediates the exaggerated
- 51 exercise pressor reflex in heart failure. *Circulation* 2005; 112: 2293–2300.
- 52
- 53 83. Wang H-J, Li Y-L, Gao L, et al. Alteration in skeletal muscle afferents in rats with chronic
- 54 heart failure. *J Physiol* 2010; 588: 5033–5047.
- 55
- 56
- 57 84. Amann M, Venturelli M, Ives SJ, et al. Group III/IV muscle afferents impair limb blood in
- 58 patients with chronic heart failure. *Int J Cardiol* 2014; 174: 368–375.
- 59
- 60
- 61
- 62
- 63
- 64
- 65

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65
85. Van Iterson EH, Johnson BD, Joyner MJ, et al. Vo<sub>2</sub> kinetics associated with moderate-intensity exercise in heart failure: impact of intrathecal fentanyl inhibition of group III/IV locomotor muscle afferents. *Am J Physiol Heart Circ Physiol* 2017; 313: H114–H124.
  86. Gagnon P, Bussi res JS, Ribeiro F, et al. Influences of spinal anesthesia on exercise tolerance in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012; 186: 606–615.
  87. Donaldson AV, Maddocks M, Martolini D, et al. Muscle function in COPD: a complex interplay. *Int J Chron Obstruct Pulmon Dis* 2012; 7: 523–535.
  88. F lster S, Tacke M, Sandek A, et al. Muscle wasting in patients with chronic heart failure: results from the studies investigating co-morbidities aggravating heart failure (SICA-HF). *Eur Heart J* 2013; 34: 512–519.
  89. Supinski GS, Callahan LA. Diaphragmatic free radical generation increases in an animal model of heart failure. *J Appl Physiol Bethesda Md* 1985 2005; 99: 1078–1084.
  90. Meyer FJ, Borst MM, Zugck C, et al. Respiratory muscle dysfunction in congestive heart failure: clinical correlation and prognostic significance. *Circulation* 2001; 103: 2153–2158.
  91. Chiappa GR, Roseguini BT, Vieira PJC, et al. Inspiratory muscle training improves blood flow to resting and exercising limbs in patients with chronic heart failure. *J Am Coll Cardiol* 2008; 51: 1663–1671.
  92. Sheel AW, Boushel R, Dempsey JA. Competition for blood flow distribution between respiratory and locomotor muscles: implications for muscle fatigue. *J Appl Physiol Bethesda Md* 1985 2018; 125: 820–831.
  93. Downing J, Balady GJ. The role of exercise training in heart failure. *J Am Coll Cardiol* 2011; 58: 561–569.
  94. Piepoli MF, Conraads V, Corr  U, et al. Exercise training in heart failure: from theory to practice. A consensus document of the Heart Failure Association and the European Association for Cardiovascular Prevention and Rehabilitation. *Eur J Heart Fail* 2011; 13: 347–357.
  95. Notarius CF, Millar PJ, Keir DA, et al. Training heart failure patients with reduced ejection fraction attenuates muscle sympathetic nerve activation during mild dynamic exercise. *Am J Physiol Regul Integr Comp Physiol* 2019; 317: R503–R512.
  96. Wang H-J, Zucker IH, Wang W. Muscle reflex in heart failure: the role of exercise training. *Front Physiol* 2012; 3: 398.
  97. Piepoli M, Clark AL, Volterrani M, et al. Contribution of muscle afferents to the hemodynamic, autonomic, and ventilatory responses to exercise in patients with chronic heart failure: effects of physical training. *Circulation* 1996; 93: 940–952.

- 1
- 2
- 3
- 4 98. Mancini DM, Henson D, La Manca J, et al. Benefit of selective respiratory muscle training
- 5 on exercise capacity in patients with chronic congestive heart failure. *Circulation* 1995; 91:
- 6 320–329.
- 7
- 8
- 9 99. Winkelmann ER, Chiappa GR, Lima COC, et al. Addition of inspiratory muscle training to
- 10 aerobic training improves cardiorespiratory responses to exercise in patients with heart
- 11 failure and inspiratory muscle weakness. *Am Heart J* 2009; 158: 768.e1–7.
- 12
- 13
- 14 100. Laoutaris ID, Dritsas A, Brown MD, et al. Effects of inspiratory muscle training on
- 15 autonomic activity, endothelial vasodilator function, and N-terminal pro-brain natriuretic
- 16 peptide levels in chronic heart failure. *J Cardiopulm Rehabil Prev* 2008; 28: 99–106.
- 17
- 18
- 19
- 20
- 21
- 22
- 23
- 24
- 25
- 26
- 27
- 28
- 29
- 30
- 31
- 32
- 33
- 34
- 35
- 36
- 37
- 38
- 39
- 40
- 41
- 42
- 43
- 44
- 45
- 46
- 47
- 48
- 49
- 50
- 51
- 52
- 53
- 54
- 55
- 56
- 57
- 58
- 59
- 60
- 61
- 62
- 63
- 64
- 65

# Figure caption

**Fig. 1** putative mechanisms responsible for the exercise intolerance and early fatigue induced by type III/IV afferent feedback in chronic heart failure. Abnormal central abnormal hemodynamics initiate a cascade which ultimately result in an increase in III/IV afferents feedback activity. It is to be highlighted that physical training may potentially counteract this malfunctioning at various levels, while, to date, no pharmacological intervention has been demonstrated able to correct this abnormal regulation.

**Figure 1**